58258T HBD.

= FR 2.126.270

PATENT SPECIFICATION

(11) **1351409**

1351409

(21) Application No. 8395/72 (22) Filed 23 Feb. 1972
(31) Convention Application No. 118081 (32) Filed 23 Feb. 1971 in
(33) United States of America (US)
(44) Complete Specification published 1 May 1974
(51) International Classification A61K 27/12 7/00//C09K 3/30
(52) Index at acceptance
A5B 244 246 24Y 351 35Y 381 385 38Y 390 391 392 396 39X 734 751 754 757 771
C4X 11

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(19)

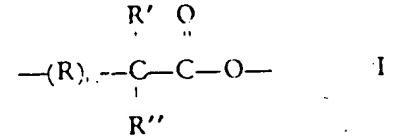
(54) SUSTAINED RELEASE PHARMACEUTICAL COMPOSITIONS FOR TOPICAL APPLICATION

(71) We, E. I. DU PONT DE NEMOURS AND COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, of Wilmington, Delaware 19898, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel polymer-drug formulations and to their use in bringing about desired biological effects when applied topically to living organisms, particularly human beings and warm-blooded animals such as domestic animals and pets.

U.S. Patent 3,297,033 discloses polyhydroxyacetic acid made into absorbable surgical devices such as sutures and filaments having controlled strength characteristic. It does not teach the concept of a topical polylactide-drug composition for releasing drug to a desired external site at a controlled rate where the polymer is derived predominantly from lactide.

According to one feature of the present invention there are provided pharmaceutical compositions for topical application comprising at least one drug (as hereinafter defined) in association with a polymer containing repeating units of the formula



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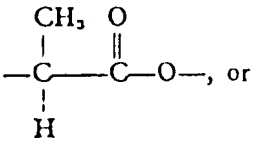
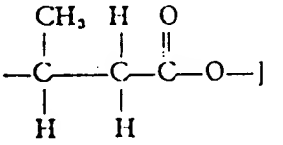
[wherein R is a lower alkylene roup of up to 6 carbon atoms; m is 0 or 1; R' is a hydrogen atom or a lower alkyl group containing up to 6 carbon atoms; R'' is a hydrogen atom or an alkyl group containing up to 22 carbon atoms when m is 0, or a hydrogen atom or an alkyl group containing up to 6 carbon atoms when m is 1; R' and R'' are the same or different; and at least 40 % by weight of the polymer consists of the repeating unit

a)  , or

b) 

the proportions of the drug and the polymer and the association between the drug and the polymer being such that upon topical application of the composition there is sustained release of the drug over a period of time.

According to a further feature of the invention, there is provided a method of preparing pharmaceutical compositions according to the invention as hereinbefore defined which comprises combining the drug and the polymer with at least one pharmaceutical carrier, excipient or diluent whereby a pharmaceutical composition for topical application is produced.

According to a still further feature of the invention, there is provided a particulate composition for use in the preparation of pharmaceutical compositions which comprises a drug (as hereinafter defined) in association with a polymer as hereinbefore defined, the preparation of the drug and the polymer and the association between the drug and the polymer being such that the composition is of use in the formulation of sustained release pharmaceutical compositions for topical application.

In the pharmaceutical compositions according to the invention, the polymer may be generally described as a polylactide. The pro-

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portions of drug and polylactide generally range from 0.01% by weight of drug and 99.99% by weight of polylactide to 90% by weight of drug and 10% by weight of polylactide. The compositions may if desired, contain a suitable solvent, diluent or dispersing agent and optionally a propellent. When applied to living tissue by conventional means such as spraying, brushing, rolling, or swabbing, and following removal of volatile diluent or solvent by evaporation, the resulting intimate mixture of polylactide and drug forms an adherent, pharmaceutically useful, medicated film. In such a film the polylactide may be considered as a carrier or matrix for the drug, and is designed to release effective amounts of the drug over a predetermined period of time.

The medicated films have the valuable characteristic of undergoing gradual hydrolysis to release the drug and form physiologically normal substances. They do not, for example, have to be removed from burns, blisters, or open wounds but rather are absorbed slowly. If desired, such films can also be removed by washing with warm water, or they can simply be allowed to sluff off as their polymer components are decomposed by the hydrolytic action of tissue fluids and moisture. Like conventional medicated dressings, these polylactide-drug medicated films also serve to seal and protect lesions as well as to hold a drug in intimate contact with the area to be treated. However, they are more convenient, more comfortable, and cosmetically more acceptable than conventional dressings. Compositions of the invention that contain a propellent and are applied by spraying constitute a preferred embodiment. Further preferred are sprayable compositions containing an antibiotic agent, an anti-inflammatory agent, or mixtures of both.

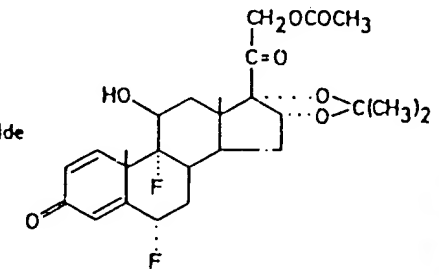
The term "drug" is intended in its broadest sense as defined in the United States Federal Food Drug and Cosmetic Act Section 201(2)g:

1. articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement of any of them; and
2. articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
3. articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
4. articles intended for use as a component of any article specified in clause 1, 2 or 3; but does not include devices or their components, parts, or accessories.

Classes of drugs that may be specifically mentioned include antibacterials, such as benzalkonium chloride and benzyl benzoate; antibiotics, such as bacitracin and neomycin; antifungals, such as tolnftate, selenium sulfide and zinc undecylenate; antihistamines, such as diphenhydramine hydrochloride; antiinflammatories, such as hydrocortisone; antiparasitics, such as chlorphenanthane; antiperspirants, such as aluminum chloride hexahydrate; antipruritics, such as methanol and camphor; contraceptives; deodorants; drugs which promote healing, such as balsams and steroid anabolic agents; enzymes, such as fibrinolysin and desoxyribonuclease; hormones, such as estradiol 17β - enanthate; local anesthetics, such as xylocaine and benzocaine; rubifacients, such as methyl salicylate.

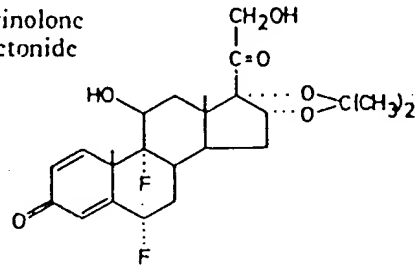
Examples of commercial fluorocorticoid antiinflammatories which can be used in the practice of the invention are the following:

Fluocinolide



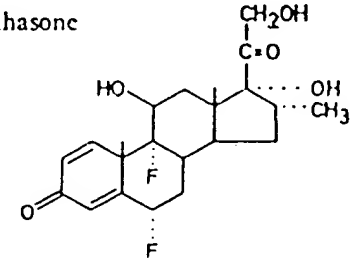
6α,9α - Difluoro - 11β,16α,17α,21 - tetrahydroxypregna - 1,4 - diene - 3,20 - dione 21 - acetate 16,17 - acetonide

fluocinolone acetonide



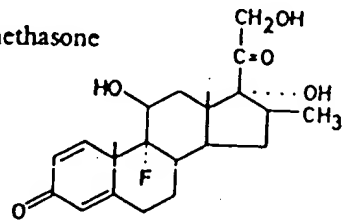
6α,9α - Difluoro - 11β,16α,17α,21 - tetrahydroxypregna - 1,4 - diene - 3,20 - dione 16,17 - acetonide

Flumethasone



6α,9α - Difluoro - 16α - methyl - 11β,17α, 21 - trihydroxypregna - 1,4 - diene - 3,20 - dione

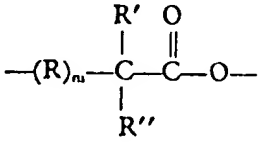
Betamethasone



9α - Fluoro - 16β - methyl - 11β,17α,21 - trihydroxypregna - 1,4 - diene - 3,20 - dione.

As indicated above, the polymers employed in the compositions according to the present invention may be designated as "polylactides" which term is used herein in both its generic sense to include polymers of an intermolecular cyclic ester formed by the condensation of two molecules of an α - hydroxy acid, and also in its specific sense to include the polymers of the intermolecular cyclic ester formed by the condensation of two molecules of lactic acid (α - hydroxypropionic acid). The meaning in any given situation will be evident to one skilled in the art.

Preferred polymers for use in the compositions according to the invention are those consisting essentially of repeating units of the formula



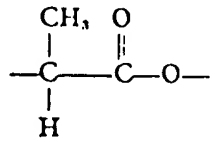
wherein R is a methylene (—CH_2—), ethylene

(—CH_2—CH_2—)

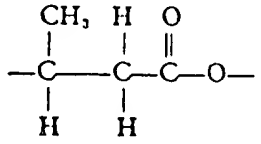
or ethylidene

(—$CH(CH_3)$—

group; R′ is a hydrogen atom or a methyl or ethyl group; and m and R″ are as hereinbefore defined, at least 40%, by weight of the polymer consisting of the repeating unit

a) 

derived from lactic acid, or

b) 

derived from β - hydroxybutyric acid.

Preferred, because of availability of starting materials, are lactide comonomer repeating units derived from α - hydroxycarboxylic acids, i.e. units of the above formula in which m is 0. It will be seen that when m is 0, R′ is methyl and R″ is H, the formula describes a repeating unit derived from lactic acid.

Further preferred because of their greater solubility in a range of solvents are polymers in which at least 70% by weight of the polymer consists of the aforesaid repeating unit derived from lactic acid or β - hydroxybutyric acid.

When R′ and R″ are different, the hydroxy acid from which the repeating unit is derived, and therefore the unit itself, can exist in optically active (D- and L-) forms or in optically inactive (DL-, racemic) form. For example, repeating units derived from lactic acid, considered either as the principal polymer component or as the comonomer component, can be present as D-lactide units, L-lactide units, or DL-lactide units. For example, a polymer containing both L-lactide and DL-lactide repeating units is defined in the present invention as a copolymer, e.g., an L-lactide/DL-lactide copolymer.

Illustrative of the comonomers which can be employed with lactide to form copolymers useful in preparing the formulations of this invention are β - propiolactone, glycolide, tetramethylglycolide, β - butyrolactone (derived from β - hydroxybutyric acid), γ - butyrolactone, pivololactone, and intermolecular cyclic esters of α - hydroxybutyric acid, α - hydroxyisobutyric acid, α - hydroxyvaleric acid, ε - hydroxyisovaleric acid, α - hydroxycaproic acid, α - hydroxy - α - ethylbutyric acid, α - hydroxyisocaproic acid, ε - hydroxy - β - methylvaleric acid, α - hydroxyheptanoic acid, ε - hydroxyoctanoic acid, α - hydroxydecanoic acid, α - hydroxymyristic acid, α - hydroxystearic acid, ε - hydroxylignoceric acid and the like.

In addition to being usable as a comonomer, β - butyrolactone can be used as the sole monomer or as the principal monomer along with any of the comonomers recited above, i.e., poly - β - butyrolactone and copolymers thereof can be used as polymers in the formulations of the invention. The term polylactide as used herein is intended to include poly - β - butyrolactone and copolymers of β - butyrolactone with the comonomers recited in the immediately preceding paragraph. The preferred sole monomer or principal monomer is lactide.

Where lactic acid is used to prepare the polymer, it is clear that the polymer's hydrolysis products will include lactic acid which is a normal metabolite of the body. Where the polymer is prepared from the other compounds listed above, the hydrolysis products will be related in structure to those derived

from lactic acid polymers and will have no deleterious or untoward effect on the body.

In preparing the polymers and copolymers from which the formulations of this invention are made, the appropriate intermolecular cyclic esters (generically, lactides) or intramolecular cyclic esters (lactones) of the hydroxy acids may be used. Intermolecular cyclic esters containing six-membered rings, e.g., glycolide, are usually used to introduce repeating units derived from alpha - hydroxy acids. Monomeric lactones, e.g., β - propiolactone and γ - butyrolactone, are usually used to introduce repeating units derived from β- or γ-hydroxy acids.

The polymerization is effected by heating the lactide above its melting point in the presence of a polyvalent metal oxide or compound thereof, under anhydrous conditions in an inert atmosphere.

Specially useful catalysts are zinc oxide, zinc carbonate, basic zinc carbonate, diethylzinc, tributylaluminum, titanium, magnesium or barium compounds, litharge, and the like.

The amount and type of catalyst used determine the particular temperature and time required to produce polymer useful for conversion to the formulations of this invention. Thus, the amount of catalyst can be as low as 0.01 weight percent or as high as 2 weight percent of the total weight of reactants. As a rule, the lower the amount of catalyst, the longer the time required to produce polymer of a given inherent viscosity and, conversely, the higher the catalyst concentration, the shorter the time. The best balance is usually obtained employing from 0.02 weight percent to 1 weight percent of catalyst.

In general, it is desirable to agitate the reaction mixture continuously during the polymerization in order to produce a homogeneous polymer at good conversions and to conduct the reaction in two steps, the first being carried out at a lower temperature than the second, or finishing step. Other methods, such as those disclosed in U.S. Patents 2,703,316 and 2,758,987, can be used in making the polymers. The degree of polymerization can be varied over a considerable range. In general, the higher the degree of polymerization, that is, the higher the molecular weight of the polylactide, the slower is its rate of absorption, etc. in the body and the slower will be the rate of release of its associated drug. Polymers that are polymerized to the extent of being solids are generally preferred.

The following is an example of a method for preparing a polymer or copolymer useful in the formulations of this invention: Lactide, which is the intermolecular ester derived from 2 moles of lactic acid, is purified by several crystallizations from carbon tetrachloride and placed either alone in the case of homopolymerization, or with one or more comonomers in case of copolymerization, in a thoroughly dried reactor equipped with a stirrer and nitrogen inlet tube. Dry nitrogen is introduced immediately above the reaction mixture and heating and stirring are started. When the temperature of the reaction mixture has reached about 100°C., the nitrogen inlet is replaced by a thermometer, and from about 0.01 to 2 weight percent of an oxide or salt of a Group II metal of atomic number 12 through 56, or litharge is added. In the case of polymerization with a liquid comonomer the liquid comonomer is preferably added after the lactide has melted. Heating is continued until polymer having the desired inherent viscosity, e.g., 0.5 to 0.1% concentration in benzene at 25°C. is obtained. This may require from a few minutes up to 25 or more hours, depending upon the catalyst used. The foregoing is not intended to be limiting since the viscosity may range from about 0.3 or less to about 4.0 or more, for example in benzene, chloroform or other suitable solvent.

Polymer, produced as above, may be suitably further treated by cutting it into small pieces, dissolving in a suitable solvent, for example, benzene, toluene or xylene, and precipitating the polymer by pouring the solution into a large volume of a nonsolvent for the polymer, desirably hexane or methanol. The precipitated polymer is removed by filtration, transferred to a blender and a nonsolvent for the polymer is added. The blender is started and after a homogeneous dispersion has been obtained, the dispersion is filtered. The polymer is allowed to dry on the filter, and is then transferred to a vacuum oven. After drying overnight at 100°C., the polymer is removed from the oven and allowed to cool at ambient temperature.

Commercially available organic solvents or mixtures thereof can be used to prepare the formulations of the invention. Those skilled in the art of polymer handling and of drug formulation can readily determine, with minimum experimentation, a suitable solvent system for use with any given polylactide-drug combination of the invention.

The solubility of the polylactide depends to some extent on its structure. Poly - L - lactide is soluble in chloroform. Poly - DL - lactide is soluble in this solvent and also in dioxane, butyl acetate, tetrahydrofuran, methyl ethyl ketone, cyclohexanone, benzyl alcohol, dimethyl carbonate, and ethyl chloride. Copolymers in general are soluble in a wider variety of solvents than are homopolymers. For example, lactide/glycolide copolymers containing a predominant amount of lactide constituent are soluble in most or all of the solvents mentioned above and also in acetone and ethyl acetate.

In addition, as is well known to one skilled in the art, the solubility of a polylactide will

depend on its molecular weight. In general, polylactides of relatively lower weights will be more soluble in particular solvents and will be soluble in a greater variety of solvents.

Inert propellents for use in spray formulations are well known in the art. One versed in the field of aerosol technology will be readily able to select a propellent suitable for use with a given polymer-drug-diluent mixture, as set out for example in the text "Principles of Aerosol Technology", Paul A. Sanders, 1970 (Van Nostrand Reinhold). The preferred propellents are low-boiling fluorohaloalkanes containing one or two carbon atoms, particularly those sold under the name Freon (Registered Trade Mark). Mixtures of more than one propellent can be used.

Suitable propellents include the following:

Formula	Approx. B.P., °C
CHF_2Cl	−41
CF_2ClCF_3	−39
CF_2Cl_2	−30
CH_3Cl	−24
CH_3CF_2Cl	−10
CF_2ClCF_2Cl	4
$CHFCl_2$	9
C_2H_5Cl	12
$CHFClCHF_2$	17

In addition, certain higher-boiling fluorohaloalkanes, not normally regarded as propellents by themselves, can be mixed with any of the propellents discussed above to lower the overall pressure of the mixture. An example is $CFCl_3$, B.P. 24°C.

In some cases a single compound can function both as a solvent and as a propellent. An example is ethyl chloride.

The drug, the polymer, the solvent or diluent, optionally the propellent, and optionally one or more other additives discussed below can be mixed by any of a number of conventional methods.

Coating, embedding or intimately mixing the drug compound with the polymer can be accomplished in the following ways:

A. Coating the discrete drug particles or drug-particle aggregates, agglomerates or flocs by:

1. Spray drying

Finely divided drug particles are suspended in a solvent system in which the drug is not soluble containing the dissolved polymer and other agents, e.g., extenders, plasticizers, dyes, etc., in the drug/polymer ratio from 1/59 to 99/1, followed by spray drying. For example: Drug particles 0.2 to 10 microns in size and equal to the weight of polymer used as suspended in a chloroform solution of polymer in such a concentration as to give a liquid viscosity suitable for atomizing. The drug-polymer mixture is spray-dried using conventional methods of atomizing, e.g., centrifugal wheel, pressure and two-fluid nozzle using appropriate drying conditions and temperatures that do not exceed the softening point of the polymer and do not exceed the melting point or decomposition point of the drug.

2. Pan coating or fluid-bed coating

Place granules or pellets, 5 microns to 20 mm., preferably between 0.25 and 10 mm. diameter, in a rotating coating pan or fluid-bed drier, and apply polymer (dissolved in a carrier to a suitable viscosity for spraying) by spraying until a suitable coating quantity has been deposited to give the required release-rate characteristics. For example: Granules of drug are prepared by extrusion of a wet granulation or other suitable methods known to the art, and dried. 16-to-40-Mesh granules are placed in a rotating coating pan and a solution of polymer, dissolved in a suitable nonaqueous volatile solvent, is sprayed onto the moving granules with a continuous fine spray under conditions known to the art, until a coating giving the desired release rate has been applied. The granules are then dried.

3. Micro-encapsulation

Suspend drug particles, granules or pellets (.1 to 2000 microns diameter) in a solvent system in which the drug is not soluble, and which contains in solution the polylactide or polylactide mixture. Add an agent incompatible with the polymer-solvent system, such as an incompatible polymer, a nonsolvent for the polymer, or a salt, or vary conditions such as temperature and pressure. One or a combination of the above will precipitate the polymer, coating the drug particles, granules or pellets. For example, 0.5-to-25-micron drug particles are suspended in chloroform (in which they are not soluble) containing the polylactide polymer mixture in solution at such a concentration as to give a low-viscosity solution. A miscible solvent in which the polymer is not soluble, such as hexane, is then added slowly to precipitate the polymer. The coated particles are filtered and washed with hexane and allowed to dry.

B. Embedding

The polymer or polymer mixture is melted and a nonheat-labile drug is suspended and thoroughly dispersed in the melt. The melt is congealed by spraying, or in a mass and ground into small particles to give a polymer matrix with the drug embedded. For example the polylactide polymer mixture is melted and 0.5-to-400-micron (preferably 0.5-to-25-micron) drug particles are suspended and thoroughly dispersed in the molten polymer in a concentration necessary to give the desired release rate patterns. The polymer is

congealed by cooling in a mass and ground into small pieces 1 to 200 microns in size.

C. Intimate Mixing

The drug and polymer are dissolved in a common solvent and the solvent is removed in some suitable way (spray-drying, flash-evaporation, etc.). For example: the drug and polylactide polymer are dissolved in chloroform in a 1:1 ratio and to a concentration of 2% in the solvent. The solvent is flash-evaporated and the resulting film is scraped from the flask and powdered.

The above sustained-release powder, granular or pellet forms, may be included in the following type formulations:

1. Suspensions

Active ingredients of low solubility which have been embedded in or coated with the polymer and are in a finely divided state, 200 microns diameter or less, preferably 50 microns or less, may be suspended in a suitable pharmaceutical vehicle. This vehicle may also contain suspending and thickening agents, e.g., methylcellulose, and preservatives. These ingredients are combined to give a stable suspension which will release the active ingredient over the time period desired.

2. Emulsions

Active ingredients insoluble in oil in fine powder form, preferably 10 microns or less, are thoroughly dispersed in a suitable oil, which is, in turn, emulsified in an external aqueous phase (oil in water) using suitable emulsifying agents, e.g., triethanolamine oleate, polyoxyethylene sorbitan monooleate, acacia, gelatin, etc. The aqueous phase may also contain agents such as protective colloids and preservatives, formulated to give a stable emulsion which will provide a controlled release of the active ingredient over the time period desired.

3. Aqueous suspensions

The active ingredient embedded and/or coated with the polymer in a particle size no greater than 200 microns and preferably no greater than 50 microns is suspended in an aqueous solution which may contain thickening agent, e.g., carboxymethylcellulose; preservatives, e.g., phenol; suspending agents, e.g., polyvinylpyrrolidone; surface active agents; buffers and dextrose or saline to adjust for isotonicity.

4. Non-aqueous suspensions

The active ingredient embedded and/or coated with the polymer in a particle size usually no greater than 200 microns and preferably no greater than 50 microns is suspended in a suitable oil, e.g., sesame oil, peanut oil, vegetable oil, etc. The suspension may contain preservatives, e.g., chlorbutanol or methylparaben and propylparaben mixtures, and suspending agents such as aluminum monostearate.

In both the aqueous and non-aqueous preparations, processing will be such that the final product will be sterile and will meet all sterility test standards.

For sustained-release dermatological formulations, the drug, imbedded or coated with the polymer by methods described above, is thoroughly dispersed in a suitable ointment base, cream, or lotion. The mixtures may contain emolients, essential oils, dyes, fillers, sun-screening agents, and/or thickening agents, and the like, that are compatible with the other components.

For preparations to be sprayed onto living tissue, the drug, if in powder form coated with polymer, should be no greater than 10 microns in diameter. This powder may be formulated to be dispersed in a suspension or dispersion system or in a quick-breaking foam. The drug may also be suspended in a nonsolvent or propellent containing the dissolved polymer, so that the drug particles are coated while being dispensed by the spray. Intimate mixing and sustained release may also be obtained if both drug and polymer are dissolved in a common solvent or solvent mixture. Continuous sprays or metered-dose sprays may be used, depending on dosage requirements. Sprayable solutions may contain compatible additives of the types mentioned in the preceding paragraph.

The formulations of the invention may contain pharmaceutically acceptable inert additives such as plasticizers and carriers. Examples are propylene glycol, Carbowax (Registered Trade Mark) polyethylene glycols, glycerides, and ethyl cellulose. Very low molecular weight polylactides, or even the monomeric acids (e.g. lactic acid) are particularly useful for softening a high-molecular-weight polylactide matrix, making it more adhesive and flexible without sacrificing biodegradability.

The relative proportions of the drug and the polymer can be varied over a wide range, depending on the desired effect. Proportions may range from 0.01% of drug and 99.99% of polymer to 90% of drug and 10% of polymer. Ratios that have shown good results include one part of drug to from 4—20 parts of polymer.

Polymer/solvent ratios will be determined to some extent by the inherent viscosity of the polylactide chosen. In general polylactide solutions containing from 1 to 20% by weight of polymer in solvent are suitable; higher concentrations tend to be too viscous for spraying. The amount of propellent employed will depend on its boiling point and solvent characteristics and can range all the way from 99% propellent with 1% polymer when the propellent is also the solvent, to 10% propellent, 90% solvent when the propellent is

very low boiling and a poor solvent for the polymer or drug.

The following examples illustrate the products and processes of the invention. All parts are by weight unless stated otherwise.

Example 1

One gram of lactide/glycolide (70/30) copolymer, prepared according to the general procedure mentioned above, was dissolved in 48 ml of chloroform. The polymer had an inherent viscosity of about 2.31 at 0.1% in chloroform at 30°C. Prednisolone (1,4 - pregnadiene - 3,20 - dione - 11β,17α,21 - triol) (5 mg) was dissolved in 25 ml of this solution. A portion of the polymer-drug solution was sprayed onto the skin of the forearm of an adult human male by means of an aerosol spray apparatus ("Spray-eze" Registered Trade Mark) containing CF_2Cl_2 as the propellent. This left an adherent film containing 1% by weight of steroid. It was adherent, flexible, comfortable, transparent, and it was more durable than a common ointment formulation, which is messy and subject to adventitious removal.

Example 2

The polymer-drug solution of Example 1 was mixed with a small amount of propylene glycol (5% by wt. of the polymer) and sprayed as in Example 1 onto the skin of the forearm of an adult human male giving a film which was judged to be more flexible than the film obtained in Example 1.

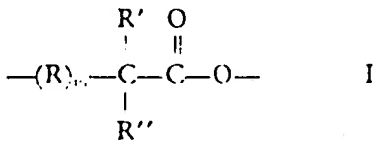
Example 3

One-half gram of each of three samples of poly - DL - lactide was dissolved in a solution of 5.0 mg. of prednisolone in 49.5 ml. of ethyl acetate. A portion of each of the resulting polymer-drug solutions was sprayed onto a glass surface by the method of Example 1. The properties of the starting polymers and of the films are summarized in the following table.

Polymer		
Inherent Viscosity (0.1%, in benzene)	Molecular Weight (By gel permeation chromatography)	Properties of Film
1.50	240,000	Tough, clear, slightly elastic
0.50	41,000	Less tough, clear, slightly sticky
0.36	32,000	Also less tough, clear, slightly tacky

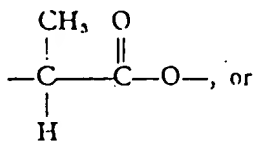
WHAT WE CLAIM IS:—

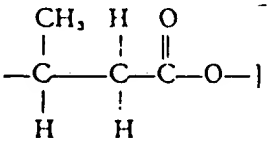
1. Pharmaceutical compositions for topical application comprising at least one drug (as hereinbefore defined) in association with a polymer containing repeating units of the formula



I

[wherein R is a lower alkylene roup of up to 6 carbon atoms; m is 0 or 1; R′ is a hydrogen atom or a lower alkyl group containing up to 6 carbon atoms; R″ is a hydrogen atom or an alkyl group containing up to 22 carbon atoms when m is 0, or a hydrogen atom or an alkyl group containing up to 6 carbon atoms when m is 1; R′ and R″ are the same or different; and at least 40% by weight of the polymer consists of the repeating unit

a)  , or

b) 

the proportions of the drug and the polymer and the association between the drug and the polymer being such that upon topical application of the composition there is sustained release of the drug over a period of time.

2. Compositions as claimed in claim 1 comprising 0.01 to 90% by weight of the said drug and 10 to 99.99% by weight of the said polymer, the said percentage being based upon the total weight of drug and polymer.

3. Compositions as claimed in claim 1 or claim 2 wherein the polymer contains repeating units of formula I wherein R represents a methylene, ethylene or ethylidene group, and R′ represents a hydrogen atom or a methyl or ethyl group.

4. Compositions as claimed in claim 1 or claim 2 wherein the polymer is derived from an α - hydroxy - carboxylic acid.

5. Compositions as claimed in claim 1 or claim 2 wherein the polymer comprises at least 70% of repeating units a) or b) derived from lactic acid or β - hydroxy - butyric acid respectively.

6. Compositions as claimed in claim 5 wherein the polymer is a homopolymer consisting essentially of repeating units a).

7. Compositions as claimed in claim 1 or claim 2 wherein the polymer is a homopolymer consisting essentially of repeating units b).

8. Compositions as claimed in claim 1

or claim 2 wherein the polymer is a copolymer of lactide and glycolide.

9. Compositions as claimed in any of the preceding claims wherein the drug comprises an anti-inflammatory agent, an antibacterial agent, antibiotic, antifungal agent, antihistamine agent, antiparasitic agent, antiperspirant agent, antipruritic agent, contraceptive, deodorant, enzyme, hormone, local anaesthetic or rubifacient.

10. Compositions as claimed in claim 9 wherein the said anti-inflammatory agent comprises 1,4 - pregnadiene - 3,20 - dione - 11β,17α,21 - triol.

11. Compositions as claimed in any of the preceding claims also containing one or more pharmaceutical carriers, excipients or diluents.

12. Compositions as claimed in claim 11 in the form of a solution of the drug and polymer.

13. Compositions as claimed in claim 12 adapted for use in aerosols and containing at least one propellent.

14. Compositions as claimed in claim 13 wherein the propellent comprises a halogenated hydrocarbon.

15. Compositions as claimed in claim 14 wherein the halogenated hydrocarbon is a fluorochloro - alkane containing 1 or 2 carbon atoms.

16. Compositions as claimed in claim 11 in the form of a suspension or emulsion of the drug in particulate form.

17. Compositions as claimed in claim 16 wherein the drug particles are in powder, granular or pellet form.

18. Compositions as claimed in claim 16 or claim 17 wherein the drug particles are coated with the polymer.

19. Compositions as claimed in claim 16 or claim 17 wherein the drug particles are embedded in the polymer.

20. Compositions as claimed in any of claims 16 to 19 wherein the particle size of the drug particles is not greater than 50 microns.

21. Compositions as claimed in claim 20 wherein the said particle size is not greater than 10 microns.

22. Compositions as claimed in any of claims 4 and 16 to 21 in the form of ointments, creams or lotions.

23. Compositions as claimed in any of the preceding claims containing the drug and the polymer in a ratio by weight of between 1 : 4 and 1 : 20.

24. Compositions as claimed in claim 1 substantially as herein described.

25. Compositions as claimed in claim 1 substantially as herein described in any of the Examples.

26. A method of preparing pharmaceutical compositions as claimed in any of the preceding claims which comprises combining the drug and the polymer with at least one pharmaceutical carrier, excipent or diluent whereby a pharmaceutical composition for topical application is produced.

27. A method as claimed in claim 26 wherein the drug is in particulate form.

28. A method as claimed in claim 27 wherein the drug particles are coated with the polymer.

29. A method as claimed in claim 27 wherein the drug particles are embedded in the polymer.

30. A method as claimed in claim 26 wherein the said polymer and the said drug are dissolved or suspended in a pharmaceutical diluent comprising a propellant to form a composition adapted for use in aerosols.

31. A method of preparing pharmaceutical compositions as claimed in any of claims 26 to 30 substantially as herein described.

32. A method of preparing pharmaceutical compositions as claimed in any of claims 26 to 30 substantially as herein described in any of the Examples.

33. Pharmaceutical compositions whenever prepared by a process as claimed in any of claims 26 to 32.

34. A particulate composition for use in the preparation of pharmaceutical compositions which comprises a drug (as herein defined) in association with a polymer as defined in claim 1, the proportions of the drug and the polymer and the association between the drug and the polymer being such that the composition is of use in the formation of sustained-release pharmaceutical compositions for topical application.

35. A composition as claimed in claim 34 when the polymer is as defined in any of claims 3 to 8.

36. A composition as claimed in claim 34 or claim 35 wherein the drug is as defined in claim 9 or claim 10.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1974.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

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